REMARKS

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-128, and 142-192 were pending in this application before entry of the amendments made herein. Claims 124-126, 169-178 and 192 have been withdrawn by the Examiner as being drawn to non-elected inventions.

Applicant has amended claims 62, 179, and 192 to clarify the claimed invention. Specifically, claims 62 and 179 have been amended to recite that the amino acid sequence of the Tat mutant is SEQ ID NO:7, 8 or 9, and that the amino acid sequence of the Tat fragment is SEQ ID NO:16 or 17. Support for the amendments can be found in the specification at, *inter alia*, pages 28, 37, and 38. Claim 192 has been amended to correct an editorial error.

No new matter has been added. Upon entry of the present amendments, claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-128, and 142-192 will be pending in the present application.

I. THE CLAIM REJECTION UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

The rejection of claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, and 186 under 35 U.S.C. § 102(b) ("Section 102(b)") as allegedly being anticipated by Chang *et al.* (AIDS. 1997 Oct;11(12):1421-31, "Chang") is maintained by the Examiner. Specifically, the Examiner alleges that the claim limitation "pharmaceutically acceptable for administration to a human" "does not change the scope of the invention in that the active ingredients of the claimed product remain the same" (see Office Action, page 2, ¶3). The Examiner asserts that the instant claims are anticipated by Chang, "[s]ince the specification does not define any specific composition ingredients, in addition to the purified HIV Tat protein, that are required to be 'pharmaceutically acceptable for administration to a human' and especially since the specification clearly states that the inventor used the heparin affinity chromatography and the Tat purification protocol as described by Chang *et al.*" (see Office Action, sentence bridging pages 2 and 3). For the following reasons, Applicant respectfully disagrees.

1. The Legal Standard

a. Claim Construction

The transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements. *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42

U.S.P.Q.2d 1608, 1613 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."); *Ex parte Davis*, 80 U.S.P.Q. 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

b. Anticipation

An anticipating reference must describe and enable the claimed invention, including all the claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. *In re Spada*, 911 F.2d 705, 708, 15 U.S.P.Q.2d 1655, 1657 (Fed. Cir. 1990); *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375, 62 U.S.P.Q.2d 1917, 1921 (Fed. Cir. 2002). The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987): "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989) (holding that "[t]he identical invention must be shown in as complete detail as is contained in the...claim"). Further, the anticipating reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.* 75 F. 3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996).

It is well established that in order for a prior art reference to amount to an inherent anticipation of a claim, all the elements of the claim must *necessarily*, *inevitably*, and *always* result from the prior art disclosure and would be so recognized by one of ordinary skill in the art; mere possibilities or probabilities are not sufficient. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553-54, 220 U.S.P.Q. 303, 313-14 (Fed. Cir. 1983); *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 325-26 (C.C.P.A. 1981); *Phillips Petroleum Co. v. U.S. Steel Corp.*, 673 F.Supp. 1278, 1295 n.12, 6 U.S.P.Q.2d 1065, 1076-77 n.12 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989); *Hughes Aircraft Co. v. U.S.*, 8 U.S.P.Q.2d 1580, 1583 (Ct. Cl. 1988); *Ex parte Levy*, 17

U.S.P.Q.2d 1461, 1463-64 (B.P.A.I. 1990); *Ex parte Skinner*, 2 U.S.P.Q.2d 1788, 1788-89 (B.P.A.I. 1987). As stated by the Court of Appeals for the Federal Circuit:

> we are not persuaded that the 'effect' of the processes disclosed in [the prior art patents], an 'effect' undisclosed in those patents, would be always to inherently produce or be seen always to produce products meeting all of the claim limitations. Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references.

W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d at 1554 (citing *In re Felton*, 484 F.2d 495, 500, 179 U.S.P.Q. 295, 298 (C.C.P.A. 1973)).

It is not sufficient that a teaching of a prior art reference *could* yield a result that would anticipate the claim against which the prior art reference is applied; instead, to be anticipatory under the doctrine of inherency, the teaching of the prior art reference *must inevitably* lead to the result. As has also been stated:

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.

In re Oelrich, 666 F.2d at 581 (citing *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (C.C.P.A. 1939)). And as stated:

> The...claim is not anticipated under the doctrine of inherency....It does not flow *undeniably and irrefutably* from the express disclosures of [the prior art reference] whether anyone recognizes it or not...The [prior art reference] does not expressly or inherently disclose each element of the...claim and therefore does not anticipate it.

Hughes Aircraft Co. v. U.S., 8 U.S.P.Q.2d at 1583 (emphasis added).

2. <u>The Meaning of the Claims</u>

The composition of independent claims 62 and 179 is open-ended, since the transitional term "comprising" is recited. *See Genentech, Inc. v. Chiron Corp.*, 112 F.3d at 501. In particular, the claimed composition (a) comprises (i) an isolated Tat protein, fragment or mutant, in combination with (ii) a pharmaceutically acceptable or excipient, and (b) is pharmaceutically acceptable for administration to a human.

As previously discussed in the Amendment filed June 14, 2006, the claim limitation "pharmaceutically acceptable for administration to a human" requires the claimed

compositions to be sufficiently safe for administration to human patients such that it can be dispensed and sold as a drug, and thus it must meet the criteria for safety defined by regulatory agencies such as the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA), *i.e.*, the composition does not contain ingredients that the skilled artisan would know, based on knowledge common in the art, would result in denial of regulatory approval for marketing as a drug for humans (see discussion on pages 16-18 of the Amendment filed June 14, 2006, which is incorporated by reference herein in its entirety).

3. The Claims are Not Anticipated by Chang

Applicant respectfully submits that the Examiner has maintained the rejection based on a misunderstanding of the meaning of the claims. As explained above, while the claimed composition contains the active ingredient biologically active Tat, fragment or mutant, the composition must also be "pharmaceutically acceptable for administration to a human," *i.e.*, it does not contain any ingredients that the skilled artisan would know, based on knowledge common in the art, would result in denial of regulatory approval for marketing as a drug for humans. The term "pharmaceutically acceptable for administration to a human" does not change that active ingredient; rather, in view of the open-ended nature of the composition arising from the use of "comprising," it excludes any ingredients (*e.g.*, inactive ingredients) that would render the composition not pharmaceutically acceptable for administration to a human. It is irrelevant whether the specification defines composition ingredients in addition to the purified Tat protein.

Thus, in order to anticipate the claimed subject matter, the case law makes it clear that Chang must disclose either *explicitly* or *inherently* that the resulting Tat composition was pharmaceutically acceptable for administration to a human.

a. No Explicit Teaching in Chang

As previously discussed in the Amendment filed June 14, 2006 (see page 18, last paragraph), both purification methods of Chang fail to explicitly disclose a Tat composition that is pharmaceutically acceptable for administration to a human.

Regarding the first purification method of Chang, (as that method is referred to in the Response filed December 13, 2005), Chang is silent as to whether the resulting Tat

composition is pharmaceutically acceptable for administration to a human. Silence does not meet the legal standard for *explicit* anticipation.

Regarding the second purification method of Chang, (as that method is referred to in the Response filed December 13, 2005), Chang explicitly states that PMSF is included in the resulting Tat composition. Since PMSF is commonly known to be very toxic, the presence of PMSF would render the composition unsuitable for regulatory approval for human administration (see ¶7 of the Second Gad Declaration accompanying the Amendment filed June 14, 2006); thus, the Tat composition resulting from the second purification method of Chang would *not* be pharmaceutically acceptable for administration to a human, as required by the claims.

b. No Inherent Teaching in Chang

As previously discussed in the Amendment filed June 14, 2006 (see pages 19-20), Chang's procedures as disclosed do not *necessarily*, *inevitably*, and *always* result in a Tat composition that is pharmaceutically acceptable for administration to a human. Regarding the first purification method of Chang, the resulting Tat composition *may*, and did in fact, include acetonitrile and TFA from the high-pressure liquid chromatography (HPLC) step (see ¶6 of the Ensoli Declaration accompanying the Response filed December 13, 2005), and thus, would not *necessarily*, *inevitably*, and *always* be pharmaceutically acceptable for administration to a human, since acetonitrile and TFA are commonly known to be very toxic and the presence of acetonitrile and TFA renders the composition unsuitable for regulatory approval for human administration (see ¶5 of the Second Gad Declaration accompanying the Amendment filed June 14, 2006).

As discussed above, Chang explicitly states that PMSF is included in the Tat composition resulting from the second purification method of Chang (see ¶6 of the First Gad Declaration accompanying the Response filed December 13, 2005), and thus, the resulting Tat composition is *not* pharmaceutically acceptable for administration to a human. Clearly, the fact that the Tat composition contains PMSF means that the second purification method of Chang does *not* inherently teach a Tat composition that is pharmaceutically acceptable for administration to a human.

As explained above, and in the Amendment filed June 14, 2006, the purification methods disclosed by Chang do not meet the standard for explicit or inherent anticipation, and thus cannot anticipate the claimed subject matter. The Ensoli Declaration and First Gad

Declaration submitted with the Response filed December 13, 2005, and the Second Gad Declaration submitted with the Amendment filed June 14, 2006 show that the presence of acetonitrile/TFA or PMSF would render the resulting Tat composition not pharmaceutically acceptable for administration to a human. The declarations are entitled to consideration and some weight, since they are not on the ultimate legal conclusion at issue. *See* the Manual of Patent Examining Procedure (Eighth Edition, Revision 5, August 2006) (hereinafter, "MPEP"), § 716.01(c), subsection III, at page 700-288, col. 2, ¶3. The Examiner has not explained why any of the declarations submitted are not convincing.

Thus, the Tat proteins obtained by both purification methods disclosed by Chang are neither explicitly nor inherently disclosed by Chang to be pharmaceutically acceptable for administration to a human, as recited in claims 62 and 179. Therefore, Chang does not teach each and every element of claims 62 and 179, and thus, their respective dependent claims. For the foregoing reasons, Applicant submits that claims 62, 63, 65, 66, 68, 69, 89, 90, 93, 94, 106, 107, 128, 142-150, 152, 153, 155-159, 161, 162, 164-168, 179-183, 185, and 186, all of which require that the Tat composition be pharmaceutically acceptable for administration to a human, are novel over Chang. Withdrawal of the Section 102(b) rejection is respectfully requested.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The rejections of various claims under 35 U.S.C. § 103(a) ("Section 103(a)") as allegedly being obvious over Chang in view of (1) the web pages entitled "HIV Vaccines: Where are we Going?" (http://www.niaid.nih.gov/daids/vaccine/1998nature.htm, "Heiman"); (2) Vogel *et al.* (Vogel FR, Powell MF. 1995. A compendium of vaccine adjuvants and excipients. In: Powell MF, Newman MJ, editors. Vaccine design: The Subunit and Adjuvant Approach. Plenum, New York, "Vogel"); (3) Castignolles *et al.* (Vaccine. 1996 Oct;14(14):1353-60, "Castignolles"); (4) Ramshaw *et al.* (J Immunol Methods. 1977;18(3-4):251-5, "Ramshaw"); (5) Livingston *et al.* (J Immunol. 1997 Aug 1;159(3):1383-92, "Livingston"); or (6) Barry *et al.* (Clin Pharmacokinet. 1997 Mar;32(3):194-209, "Barry") are maintained by the Examiner. The Examiner states that the rejections are maintained for the same reason as the above Section 102(b) rejection is maintained.

1. The Legal Standard

A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and the content of the prior art, the differences between the invention and the prior art, the level of the ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. *In re O'Farrell*, 853 F.2d 894, 902-4 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). In determining obviousness, "the inquiry is not whether each element existed in prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed." *Hartness International Inc. v. Simplimatic Engineering Co.*, 819 F.2d 1100, 2 U.S.P.Q.2d 1826 (Fed. Cir. 1987).

Further, an obviousness rejection cannot be based on inherent disclosure in a prior art reference. The Court of Customs and Patent Appeals has stated that "the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966).

2. The Claims are Not Obvious in View of the References

The deficiencies in the teaching of Chang are discussed above. As previously discussed in the Amendment filed June 14, 2006 (see pages 21-22), there is no suggestion in Chang of a composition comprising an isolated Tat protein, fragment or mutant in combination with a pharmaceutically acceptable carrier or excipient, wherein the composition is *pharmaceutically acceptable for administration to a human*, as recited in claims 62 and 179. Regarding the first purification method, Chang's silence as to the HPLC solvent(s) used cannot be used as a basis for the Section 103(a) rejection, since "obviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d at 448. Regarding the second purification method of Chang, the resulting Tat composition contains PMSF, which clearly renders it *not* pharmaceutically acceptable for administration to a human, and there is no suggestion in Chang to avoid the use of PMSF.

None of Heiman, Vogel, Castignolles, Ramshaw, Livingston, and Barry cure the deficiency of Chang, because none of these references teach or suggest a composition comprising an isolated Tat protein, fragment or mutant in combination with a pharmaceutically acceptable carrier or excipient, and that is pharmaceutically acceptable for administration to a human; thus, these references do not provide the missing suggestion. Accordingly, the combination of Chang plus any of Heiman, Vogel, Castignolles, Ramshaw, Livingston, or Barry does not teach or suggest the presently claimed invention.

Moreover, none of the cited references suggest or motivate the formulation of a *biologically active* Tat in a way that would be pharmaceutically acceptable for administration to a human. To the contrary, Applicant notes that the formulation of a biologically active Tat (or mutant or fragment) into a composition that would be pharmaceutically acceptable for administration to a human is contrary to the prejudice in the prior art which is against administering a biologically active Tat, since it was believed that biologically active Tat administered to a human would enhance viral replication and/or immunosuppression (see specification, page 10, lines 4-8). Chang's suggestion about further Tat studies is consistent with this prejudice in the art, since Chang suggests that understanding Tat's "release and intercellular fate may help in the investigation of new strategies to inhibit its activity including the use of Tat as...an anti-HIV-1 vaccine [64]" (see Chang, page 1430, col. 1, ¶3). The reference cited by Chang (*i.e.*, reference 64, Goldstein G. Nat Med. 1996 Sep;2(9):960-4, "Goldstein," made of record in the Supplemental Information Disclosure Statement submitted herewith) notes that biologically active Tat is essential for HIV-1 replication, infection, and pathogenesis (see Goldstein, page 960, Abstract; and page 961, col. 1, description of Figure 1), and that transactivation by the Tat immunogen itself is a problem that can be evaded by the use of a Tat immunogen containing amino acid substitutions that block its biological (transactivation) activity (see Goldstein, page 962, col. 1, description of Figure 2).

In view of the foregoing, Applicant respectfully submits that the Section 103(a) rejections are in error and respectfully requests the Examiner to withdraw the rejections.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

1. The Claims Comply with the Written Description Requirement

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 are rejected under 35 U.S.C. § 112 ("Section 112"), first paragraph, allegedly for failing to comply with the written description requirement.

paragraph, allegedly for failing to comply with the written description requirement. Specifically, the Examiner contends that the claim limitation "fragments and mutants" encompasses a genus of peptides that are defined only by function, and that while the specification provides written description of 19 mutant Tat proteins, an inordinate number of fragment/mutant sequences are not described in the specification. The Examiner also alleges that there is no identification of any particular portion of the structure that must be conserved for the biological activity of the peptides.

As a preliminary matter, Applicant submits that the bases for the Examiner's rejection do not apply to claims 65, 92, 144, 145, 147-150, 156-159, 165, 167, 168, and 180-183, since these claims limit the Tat protein, fragment, or mutant to a wild type Tat protein, and thus the rejection of these claims is in error.

Further, although Applicant does not acquiesce with the rejection of the claims, solely to expedite prosecution, independent claims 62 and 179 have been amended to recite specific fragments and mutants disclosed on pages 28, 38 and 39 of the specification. Thus, the rejection is believed to be obviated and should be withdrawn.

2. <u>The Claims Comply with the Enablement Requirement</u>

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168, and 179-191 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a composition comprising an isolated Tat protein, allegedly does not reasonably provide enablement for a Tat protein composition that is pharmaceutically acceptable for administration to a human. The Examiner contends that:

> The...claims...encompass vaccine compositions for preventing HIV in humans, and the limitation 'fragment or mutant' encompasses a genus of inordinate number of HIV Tat species as small as three amino acids.

(see Office Action, page 7, ¶3).

Regarding HIV vaccines, the Examiner adds that a "natural immune response, consisting of antibody response and viral-specific $CD8^+$ cellular response as measured in the instant application, is not effective because HIV has evolved a number of evasion strategies" (see Office Action, page 9, ¶2), and that there is not sufficient guidance as to the clinical efficacy of the claimed composition (see Office Action, page 10, ¶2).

For the following reasons, Applicant respectfully disagrees.

a. The Legal Standard

The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph, that the specification describe (1) how to make and (2) how to use the invention. *See* MPEP § 2164. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *United States v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary, provided the experimentation required is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Jackson*, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. & Inter. 1982)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983).

By definition, undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover,* 443 F.2d 1386, 1392, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that are relevant in determining what constitutes undue experimentation as set forth by the Federal Circuit (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Inter. 1986)) include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Any conclusion of nonenablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. *In re Wands*, 858 F.2d at 740.

The Patent Office must establish a *prima facie* case of non-enablement in order to properly reject a claim on that basis. "When rejecting a claim under the enablement requirement of § 112, the Patent Office bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention in the specification of the application..." *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993).

Even when the specification discloses multiple utilities of the claimed product, an applicant need show utility for only one disclosed purpose to satisfy the utility requirement under 35 U.S.C. § 101 and 35 U.S.C. § 112. *See Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958-59, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983). When the dispositive issue is whether sufficient evidence is put forth to establish an asserted utility, the issue may be raised under 35 U.S.C. § 101 and/or 35 U.S.C. § 112. *See In re Jolles*, 628 F.2d 1322, 1326, 26 U.S.P.Q. 885, 889 (C.C.P.A. 1980). The MPEP states:

> regardless of the category of invention that is claimed (e.g., product or process), an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility.

See MPEP § 2107.02, subsection I, at page 2100-28, col. 1, ¶2. The MPEP also states:

> when a compound or composition claim is not limited by a recited use, *any* enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use...if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

See MPEP § 2164.01(c), at page 2100-189, col. 1, ¶2 (emphasis added).

b. <u>The Claims are Enabled by the Specification</u>

Regarding the aspect of the rejection based on the alleged breadth of "fragment or mutant," Applicant points out that claims 62 and 179 have been amended to specify fragments and mutants disclosed on pages 28, 38 and 39 of the specification. Thus, the limitation "fragment or mutant" does not encompasses "a genus of inordinate number of HIV Tat species as small as three amino acids," and the Examiner's rejection on this basis is obviated.

With respect to the aspect of the rejection based on the Examiner's allegation that the claims encompass vaccines for preventing and/or treating HIV, the Examiner's analysis of the *Wands* factors is not determinative of whether the presently claimed invention is enabled, since the Examiner's rejection appears to be based on an incorrect and improper reading of the claims. While the claims are directed to a product that *can* be used as a vaccine, the claimed composition is not limited to such use. The Examiner states that:

> the specification clearly states on page 1 that the present invention refers to a prophylactic and/or therapeutic vaccine anti-HIV, anti-AIDS and against tumors and syndromes associated with HIV infection. Therefore, the instant claims, when read in light of the specification, would lead one skilled in the art to conclude that the instant invention is clearly directed towards HIV vaccines.

(see Office Action, page 7, ¶2).

It is improper to import limitations from the specification into the claims. *Superguide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875, 69 U.S.P.Q.2d 1865, 1868 (Fed. Cir. 2004) ("Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment."); *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1369, 67 U.S.P.Q.2d 1947, 1950 (Fed. Cir. 2003) ("The problem is to interpret claims 'in view of the specification' without unnecessarily importing limitations from the specification into the claims."); *Altiris Inc. v. Symantec Corp.*, 318 F.3d 1363, 1371, 65 U.S.P.Q.2d 1865, 1869-70 (Fed. Cir. 2003) (Although the specification discussed only a single embodiment, the court held that it was improper to read a specific order of steps into method claims where, as a matter of logic or grammar, the language of the method claims did not impose a specific order on the performance of the method steps, and the specification did not directly or implicitly require a particular order).

Here, the Examiner is impermissibly importing a "use limitation" into the instantly claimed composition. However, the claimed composition need not be used as an HIV vaccine for successful treatment or prevention of HIV infection in humans. Instead, it may be used, for example, to induce an immune response against biologically active Tat (as taught in the specification at page 26, line 9, to page 27, line 25). It would be apparent to the skilled artisan that such an immune response would be useful, whether exhibited *either* as antibodies to Tat (*e.g.*, with use for passive immunotherapy, or with use in Enzyme-Linked ImmunoSorbent Assay (ELISA) to detect HIV; see, *e.g.*, the specification at page 98, line 31, to page 99, line 1), *or* exhibited as T cells which can be expanded *in vitro* (as taught in the specification at page 99, lines 10-14). Moreover, the claimed composition has immediate practical use in preclinical and/or clinical studies in the development of AIDS vaccines.

The specification clearly presents evidence that use of the claimed composition to generate an immune response is enabled. For example, the specification at page 27 describes immunizing mice and rabbits with Tat proteins, and detecting the presence of anti-Tat antibodies in the sera of the immunized animals. Example 4 of the specification also describes immunizing monkeys with the Tat protein of the invention, and detecting the resulting presence of specific anti-Tat IgM, IgG, and IgA antibodies, and specific anti-Tat cellular responses. If any use is enabled when multiple uses are disclosed, the utility requirement of Section 101 and Section 112 are satisfied. *See Raytheon Co. v. Roper Corp.*, 724 F.2d at 958-59; *see also* MPEP § 2164.02, at page 2100-189, ¶2. Since use to generate an immune response is a patentable utility that is enabled, the Examiner's rejection is in error.

Moreover, although not necessary to satisfy Section 112 for the claimed invention, use as a therapeutic or prophylactic vaccine for HIV is also enabled. As further proof that use in a clinical trial, use to generate an immune response, as well as use in treatment or prevention of HIV infection, are each an immediate practical utility that is clearly enabled, the Examiner's attention is respectfully directed to the Second Declaration of Barbara Ensoli, M.D., Ph.D. Under 37 C.F.R. § 1.132 (hereinafter, "Second Ensoli Declaration"), which describes the results of a human clinical trial using a claimed composition.

The results of the clinical trial, a copy of which is attached as Exhibit 2 to the Second Ensoli Declaration, were summarized in a press release dated July 5, 2005 by the Istituto Superiore di Sanità, which is the Assignee of record of this application, with the results explained and presented in detail in Paragraphs 6-25 of the Second Ensoli Declaration. The data showed that the Tat vaccine

> was very efficient at inducing both specific humoral and cellular immune responses against the Tat protein, including the induction of neutralizing antibodies against Tat. Further, this immune response was able to control HIV replication in infected volunteers, thus preventing $CD4^+$ T cell decline which is the most relevant parameter of disease progression

(see Second Ensoli Declaration, ¶26). The results lead Dr. Ensoli to conclude that the clinical trial showed that "the Tat vaccine has efficacy in the treatment and prevention of HIV infection" (see Second Ensoli Declaration, ¶27).

The clinical trial showed that a claimed composition was safe and well tolerated in all subjects in the preventive and therapeutic phase I trials, and induced both humoral and cellular immune responses (see Second Ensoli Declaration, ¶2). As described in detail in the

Second Ensoli Declaration, the clinical trial used a vaccine comprising a biologically active Tat formulated for use in humans according to good manufacturing practices (GMP) (see Second Ensoli Declaration, ¶3). The clinical trial involved a randomized, placebo-controlled, and doubled-blinded study on the effects of vaccinating HIV-1 negative (preventive protocol) and positive (therapeutic protocol) individuals with the biologically active Tat composition (see Second Ensoli Declaration, ¶¶4-5). The vaccine induced specific anti-Tat IgM, IgG and IgA antibodies in the vaccinated subjects (see Second Ensoli Declaration, ¶¶13 and 15, respectively), and *in vitro* assays demonstrated anti-Tat neutralizing activity for the antibodies (see Second Ensoli Declaration, ¶¶14 and 16, respectively). The vaccine also induced specific anti-Tat cellular immune responses in the vaccinated subjects (see Second Ensoli Declaration, ¶¶19 and 20, respectively). Furthermore, the vaccine showed the control of HIV replication and stabilization of $CD4^+$ T cell count (see Second Ensoli Declaration, ¶¶22-25). The Second Ensoli Declaration thus shows in a human clinical trial that a vaccine of the claimed invention is safe and has the ability to generate an immune response that is associated with stabilization of HIV viral load and $CD4^+$ T cell count, the two key parameters commonly used to monitor progression of HIV disease.

Moreover, Applicant points out that a person skilled in the art as of December 1, 1997, based on the teaching of the specification and knowledge common in the art as of December 1, 1997, and using only routine experimentation, could obtain a Tat composition that is pharmaceutically acceptable for administration to a human. The Examiner's attention is respectfully directed to the Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 (hereinafter, "Magnani Declaration"), which shows how a person skilled in the art as of December 1, 1997, based on the teaching of the specification and knowledge common in the art as of December 1, 1997, and using only routine experimentation, could obtain a Tat composition that is pharmaceutically acceptable for administration to a human (see Magnani Declaration, ¶¶3-12).

The specification at page 25, lines 5-26, describes various procedures which can be used for purifying a biologically active Tat protein: ion-exchange chromatography, HPLC, and heparin affinity chromatography. It would be clear to a person skilled in the art that, for therapeutic or prophylactic use of the resulting Tat composition in humans, one must avoid agents known to be very toxic in humans. Thus, such person would avoid the use of agents such as acetonitrile, TFA, and PMSF in selecting and implementing the procedures for purifying biologically active Tat.

It was commonly known in the art as of December 1, 1997 that a person skilled in the art would use a combination of purification steps instead of a single one of the purification steps to improve the purity of a protein (*e.g.*, with decrease levels of endotoxin) for human therapeutic use (see Magnani Declaration, ¶6). The skilled person, when reading the specification, and thus choosing a combination of procedures to use for purification of biologically active Tat for human therapeutic use, would clearly avoid HPLC rather than heparin affinity chromatography, due to the known unsuitability of the commonly used acetonitrile/TFA solvent system in HPLC, since such person would expect that the use of PMSF in heparin affinity chromatography could be avoided much more easily than the use of the standard solvent system of acetonitrile/TFA in HPLC (see Magnani Declaration, ¶7). Among those chromatographic procedures taught in the specification, the skilled person thus would be left with ion-exchange chromatography and heparin affinity chromatography (see Magnani Declaration, ¶7). In combining ion-exchange chromatography plus heparin affinity chromatography, such person also would know to perform the ion-exchange chromatography step before the heparin affinity chromatography step (see Magnani Declaration, ¶8). It would be a matter of routine experimentation for such person, *e.g.*, to avoid the use of PMSF in heparin affinity chromatography, for example, by expressing the biologically active Tat in a bacterial system that is deficient in proteases (see Magnani Declaration, ¶9), and/or by carrying out the initial purification step at 4°C to reduce protease activity prior to separation from proteases in the cell lysate (see Magnani Declaration, ¶10). Thus, a person skilled in the art as of December 1, 1997, based on the teaching of the specification and knowledge common in the art as of December 1, 1997, and using only routine experimentation, would know that (i) the ion-exchange chromatography and heparin affinity chromatography steps, as described in the above-identified application, could be combined to achieve improved purification over either alone, thus advantageously avoiding HPLC which involved solvents (*e.g.*, acetonitrile and TFA), the presence of which would render a Tat composition not pharmaceutically acceptable for administration to a human; and (ii) the initial steps of the purification procedures could be performed at a low temperature (*e.g.*, 4°C) and/or the proteins could be expressed in protein-deficient bacterial strains, to avoid proteolytic degradation of the Tat, thus advantageously avoiding the use of PMSF, the presence of which would render a Tat composition not pharmaceutically acceptable for administration to a human; to obtain a biologically active Tat that is pharmaceutically acceptable for administration to a human (see Magnani Declaration, ¶10).

For the foregoing reasons, Applicant submits that one skilled in the art, based on the teaching of the specification coupled with information known in the art at the time the patent application was filed, can make and use the presently claimed invention without undue experimentation. Thus, the rejection is in error and should be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: May 1, 2007

32,605 (Reg. No.)

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Enclosures